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BEHAVIOURAL OUTCOMES OF TREATMENT WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS

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Behavioural outcomes of treatment with selective serotonin reuptake inhibitors

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ABSTRACT

Mood and anxiety disorders are some of the biggest contributors to morbidity worldwide, and may be lethal. Appropriate treatment is therefore paramount. Antidepressant medications constitute the primary pharmacological treatment for these disorders, with selective serotonin reuptake inhibitors (SSRIs) as the most common type in several Western countries. While developed to treat disorders that increase the risk of violence and suicide, there is concern that SSRI treatment may in itself increase the risk for these behavioural outcomes, especially among young people.

The overarching aim of this thesis is therefore to contribute to the understanding of the risks and benefits of treatment with SSRIs in relation to severe behavioural outcomes in different age groups, including when SSRIs are combined with other central nervous system (CNS) drugs. We also document antidepressant prescription patterns in young individuals – the age group where the balance between benefits and risks of antidepressant treatment is least clear.

In study I, we described the prevalence of antidepressant use and polypharmacy of CNS drugs with antidepressants over time in children, adolescents, and young adults living in Sweden. We found that, over time, there was an increasing trend in antidepressant use and an increase in the co-prescription of antidepressants with other CNS drugs. We also found that antidepressant users had higher likelihood than population controls of collecting other CNS drug classes additionally to antidepressants.

In Study II, we investigated the hazard of conviction for violent crimes during treatment with SSRIs, including in different time periods since start and end of treatment. In a follow-up of up to 8 years, we found that the hazard of violent crime was statistically significantly elevated throughout treatment periods, and for up to 12 weeks after the end of treatment. This was true in youths as well as older adults, which adds to prior research that has found elevated risk of aggression outcomes during SSRI treatment in young adults but not older individuals.

In Study III, we explored the incidence rate of suicide attempts or deaths (suicidal behaviour) in time periods before and after initiation of SSRI treatment. We found that the month immediately prior to SSRI treatment initiation was associated with the greatest incidence rate of suicidal behaviour, that treatment periods up to one year after treatment initiation were associated with lower incidence rate compared to the month immediately before initiation, and that the incidence rate gradually decreased over treatment time. However, all treated

periods had higher incidence rates than the month one year before treatment start. These patterns were consistent across age categories, including among children and young adults.

In Study IV, we applied a data-driven screening approach to compare the incidence rate of suicidal behaviour in periods after and before initiation of additional CNS drugs during continuous SSRI treatment. We found several drugs that were associated with statistically significantly reduced incidence rate of suicidal behaviour when initiated during SSRI treatment, and only two associated with increased risk of suicidal behaviour. We found no evidence of harmful effects of combining SSRIs with additional CNS drugs. Many of the signals of reduced suicidal behaviour correspond to prior evidence; novel signals could be further investigated to evaluate the use of these drugs concurrently with SSRI treatment.

In conclusion, the presented thesis has documented: the increasing prevalence of antidepressant use and polypharmacy of antidepressants with other CNS drugs in young individuals resident in Sweden; the associations between SSRI use and violent crime and suicidal behaviour; and the impact of initiating other CNS drugs during SSRI treatment on the risk for suicidal behaviour. The findings are expected to help guide future research and clinical decision making.

LIST OF SCIENTIFIC PAPERS

I. **Lagerberg, T.**, Molero, Y., D'Onofrio, B. M., de la Cruz, L. F., Lichtenstein, P., Mataix-Cols, D., Rück, C., Hellner, C., & Chang, Z. (2019). Antidepressant prescription patterns and CNS polypharmacy with antidepressants among children, adolescents, and young adults: a population-based study in Sweden. *European Child & Adolescent Psychiatry*, *28*(8), 1137-1145.

II. **Lagerberg, T.**, Fazel, S., Molero, Y., Franko, M. A., Chen, Q., Hellner, C., Lichtenstein, P., & Chang, Z. (2020). Associations between selective serotonin reuptake inhibitors and violent crime in adolescents, young, and older adults–a Swedish register-based study. *European Neuropsychopharmacology*, *36*, 1-9.

III. **Lagerberg, T.**, Fazel, S., Sjölander, A., Hellner, C., Lichtenstein, P., & Chang, Z. (2021). Selective serotonin reuptake inhibitors and suicidal behaviour: a population-based cohort study. *Neuropsychopharmacology*, 1-7.

IV. **Lagerberg, T.**, Sjölander, A., Gibbons, R., Quinn, P., D'Onofrio, B.M., Hellner, C., Lichtenstein, P., Fazel, S. , & Chang, Z. Use of CNS drugs in combination with SSRI treatment: screening for risk of suicidal behavior. *(Manuscript)*

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- Virtanen, S., **Lagerberg, T.**, Khemiri, L., Suvisaari, J., Larsson, H., Lichtenstein, P., ... & Latvala, A. (2021). Association of selective serotonin reuptake inhibitor (SSRI) treatment with acute substance misuse outcomes. *Addiction*.

- Lavigne, J. E., **Lagerberg, T.**, Ambrosi, J. W., & Chang, Z. (2021). Study designs and statistical approaches to suicide and prevention research in real-world data. *Suicide and Life-Threatening Behavior*, *51*(1), 127-136.

- Li, L., **Lagerberg, T**., Chang, Z., Cortese, S., Rosenqvist, M. A., Almqvist, C., ... & Larsson, H. (2020). Maternal pre-pregnancy overweight/obesity and the risk of attention-deficit/hyperactivity disorder in offspring: a systematic review, meta-analysis and quasi-experimental family-based study. *International journal of epidemiology*, *49*(3), 857-875.

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LIST OF ABBREVIATIONS

ATC	Anatomical therapeutic chemical
CBT	Cognitive behavioural therapy
CI	Confidence interval
CNS	Central nervous system
CrI	Credible interval
DDI	Drug-drug interaction
DMN	Default mode network
FAERS	FDA adverse event reporting system
FDA	Food and Drug Administration (US)
HAM-D	Hamilton rating scale for depression
HR	Hazard ratio
ICD	International classification of diseases
IPTW	Inverse probability of treatment weighting
IRR	Incidence rate ratio
LISA	Longitudinal integrated database for health insurance and labour market studies
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NICE	National Institute for Health and Care Excellence (UK)
NPR	National patient register
OCD	Obsessive compulsive disorder
OR	Odds ratio
PDR	Prescription drug register
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trial
SMD	Standardized mean difference

SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TPR	Total population register

1 INTRODUCTION

Mood and anxiety disorders constitute some of the largest contributors to morbidity worldwide,[1] are associated with adverse health and functional outcomes,[2 3] and may, at their most severe, be lethal.[4 5] In Sweden, the economic burden of depression is estimated to have doubled between 1997 and 2005, to 3.5 billion euros.[6] Antidepressant medication is an important pharmacological treatment tool for these disorders, and selective serotonin reuptake inhibitors (SSRIs), first introduced in the late 1980s, are the most widely prescribed antidepressant type in most countries.[7 8] In Sweden, the use of SSRIs has increased over the last decade and a half, from an overall prevalence of 5.6% in 2006 to one of 6.4% in 2020.[9]

Despite the high prevalence of SSRI use and relatively favourable cardio-metabolic safety profile compared to earlier antidepressant types,[10] there are concerns about possible adverse outcomes of SSRIs.[11] These include physiological changes (e.g. weight gain, bleeding), sexual dysfunction,[12] and a range of behavioural outcomes, including violence and suicidality.[13] The behavioural outcomes have in particular caused concern, given that they may result in death or grave harm to the treated individual or others. On the other hand, the disorders indicating SSRI treatment may in themselves increase the risk for outcomes such as suicide.[14 15] Despite their relative rarity, severe behavioural outcomes have therefore been the focus of attention from researchers, clinicians, regulators, patients, and the public.

The present thesis sets out to document trends and patterns in prescription with antidepressants, the association between SSRI treatment and severe behavioural outcomes, as well as the impact on suicidal behaviour of adding other central nervous system (CNS) drugs to SSRI treatment.

1.1 SSRIs AS A PHARMACOLOGICAL TREATMENT OF MOOD DISORDERS

Selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB) were developed in the late 1980s to provide a safer alternative to the earlier tricyclic antidepressants (TCAs), which were developed in the 1950s, and which non-selectively target an array of monoamine pathways.[10] In contrast to TCAs, SSRIs selectively target the serotonin monoamine pathway, by blocking the action of the protein pump that transports serotonin out of the inter-neuronal synapses. This makes more serotonin available for binding with the post-synaptic serotonin receptor.[16] Fluoxetine (sold under the brand name “Prozac”) was the first marketed SSRI, launched in the US in 1988.[10 17] Since then, further types of SSRIs have been marketed,

including Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, and Sertraline, all of which are licensed for sale in Sweden.[18] The different subtypes of SSRIs have limited, but potentially clinically significant, secondary effects on other receptor sites,[10] with citalopram and escitalopram as the ones with least non-serotonin receptor binding properties.[19]

SSRIs are mainly indicated for mood disorders, and major depressive disorder (MDD, hereafter used interchangeably with "depression") specifically, though they may also be prescribed for other conditions, such as anxiety disorders, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), neuropathic pain, and narcolepsy.[18 20] However, for most mood and anxiety disorders, and particularly among the young, non-pharmacological treatment is the recommended first-line intervention for up to 8 weeks depending on the disorder type and severity.[20] If psychological interventions are deemed insufficient or do not lead to full recovery, the next recommended step is pharmacological treatment. SSRIs tend to be the first-line pharmacological treatment tool, especially among children and adolescents, where there is little evidence for the efficacy of non-SSRI antidepressants.[18 20] For adults, the guidelines are less restrictive and specific when it comes to the recommended type of antidepressants.[18 20]

1.2 PREVALENCE AND PATTERNS OF SSRI USE

The prevalence of antidepressant use has increased over the last decades in many parts of the world,[8 21-24] with SSRIs being the most common antidepressant type in most – but not all – Western countries.[8 24] In the US, there was an increase in antidepressant use among individuals aged 12 and over, from 7.7% in 1999-2002 to 12.7% in 2011-2014.[25] In 2011-2014, 68% of these users experienced treatment periods of two years or more, with about 25% of users having taken antidepressant medications for 10 years or more.[25] Across five European countries, including Denmark, there was an increase in SSRI use over the period 2001-2009 in all but two Dutch databases, despite different country-specific baseline prevalences.[8] In Sweden, the use of SSRIs in the population has increased over the last decades, from an overall prevalence of 5.6% in 2006 to one of 6.4% in 2020.[9] Antidepressant use has also increased among children and adolescents across Danish, American, British, German, and Dutch populations over 2005-2012.[26] The increasing prevalence of antidepressant use is mainly driven by higher levels of long-term use, rather than by an increase in the number of individuals initiating treatment over time.[23 27 28]

Across countries, females have about twice the prevalence of antidepressant use compared to males, [8 21 28-31] and there is a trend of increasing antidepressant use with age.[25] In Sweden, the majority of antidepressant treatment is administered in primary care among adults, while in children and adolescents (<18 years) the majority are treated in specialist care services.[24] This is similar to the situation in other European countries, e.g. Germany, [32] though in some settings children and adolescents are mainly treated in primary care, e.g. in France.[33]

1.3 EFFICACY OF SSRIs

Overall, SSRIs have been found to have some efficacy in treating depression based on published evidence, though the strength of the evidence differs between children and adolescents on the one hand and adults on the other, and debate remains regarding the extent of the efficacy. A recent network meta-analysis of double-blind randomized controlled trials (RCTs) found that SSRIs were superior to placebo for the acute treatment of adults with depression.[34] There is physiological evidence that SSRIs may alleviate the hippocampal shrinking associated with depression among adults,[35-37] and antidepressant treatment has been found to normalize default mode network (DMN) connectivity in individuals with depression.[38] In children and adolescents, a meta-analysis found that SSRIs were superior to placebo,[39] though a recent network meta-analysis of antidepressant treatment in children and adolescents, including all SSRIs apart from fluvoxamine, found that only fluoxetine was more efficacious than placebo.[40] Taken together, this suggests that SSRIs have some efficacy in treating adult depression, but that the evidence for antidepressant efficacy in children and adolescents is not clear.

Still, it should be noted that currently available trials for antidepressant efficacy have methodological limitations that have been highlighted as problematic,[41] and which may call some of the efficacy estimates into question.[41] Authors have also noted the probable existence of publication bias.[41] Further, while studies have found that SSRIs are statistically significantly superior to placebo, the absolute difference is modest. Absolute improvement is usually understood in terms of "clinical efficacy" – that is, in terms of whether the doctor or patient notices a difference in overall depression symptoms. There is no set definition of how big a difference this connotes.[41] In 2004, the UK National Institute for Health and Care Excellence (NICE) defined it as a minimum reduction of three points on the Hamilton Rating Scale of Depression (HAM-D),[42] representing a standardized mean difference (SMD) of 0.5. An empirical investigation has suggested that it may be even higher, at 0.875.[42] For

comparison, the network meta-analysis on antidepressant efficacy in adults cited above found an SMD of 0.3 (95% CrI=0.26–0.34).[34]

On the other hand, it has been pointed out that depression is heterogeneous,[43] and there have been calls to evaluate depression severity based on specific symptoms rather than the summary scores currently relied on.[44] When only the core symptoms of depression are considered (that is, measures directly related to "depressed mood"), the clinical improvement (in terms of SMD) in antidepressant arms versus controls has been found to be 0.4.[45] When only optimal dose of SSRIs is considered, the SMD has been found to be 0.5.[46]

The above discussion has focused on SSRI efficacy in depression. It should be noted that the efficacy may vary depending on the type of disorder indicating an individual for treatment. For example, SSRIs have been shown to be more efficacious in treating anxiety disorders or anxiety concurrent with depression than MDD alone in adults[47] as well as in children.[39]

1.3.1 Efficacy of SSRIs in the context of psychological treatments

SSRIs and other currently available antidepressants are not the only options for treatment of mood and other psychiatric disorders. Psychological therapies are the recommended first-line therapy for most mood and anxiety disorders, as described in section 1.1. A meta-analysis looking at children and adolescents found that there was no statistically significant difference in the impact on depression between fluoxetine treatment alone and fluoxetine in combination with cognitive behavioural therapy (CBT).[48] Other studies have found that a combination of antidepressant treatment and psychological treatments are more efficacious and/or safe in treatment of depression.[49-52] As for antidepressants, a given type of psychological treatment may be more suited to treat some psychiatric disorders than others. For example, CBT has been found to be more efficacious than antidepressant treatment in OCD.[53] Unfortunately, psychological treatments are resource intensive, and many patients with mood or anxiety disorders are offered only pharmacological treatment in clinical practice.[54]

1.4 BEHAVIOURAL OUTCOMES OF SSRIs

There has been extensive debate about possible behavioural outcomes of SSRIs, especially in children and adolescents. Potential adverse behavioural outcomes include agitation,[10] akathisia,[13] violence,[55] and suicidality.[55-57] It is possible that these are part of the same spectrum of activation-related outcomes caused by SSRI treatment (a "stimulant

continuum"),[13] though the link between them remains unclear. On the other hand, violence and suicidal behaviour events are more likely to occur in individuals with untreated or insufficiently treated psychiatric disorders – for example, individuals with depression have been estimated to have a three-fold higher odds of violent crime,[14] and about a 20 times higher rate of suicide,[15] than the general population – meaning that a reduction in the risk of these behavioural outcomes are also possible markers of treatment effectiveness or efficacy. The severe outcomes of violent crime and suicidality have attracted particular research attention due to their great costs to individuals and society.

1.4.1 Aggression and violence

While ecological studies have found a negative association between antidepressant prescription and violent crime and homicide,[58 59] evidence from multiple individual-level study designs suggest that SSRI treatment is associated with an increased risk of aggression and violence among young people, with weaker evidence regarding associations in middle-aged and older adults. A systematic review of RCTs found that the SSRI treatment group had an almost tripled odds of aggression outcomes among children and young adults compared to controls, while adults had a modestly elevated, and non-statistically significant, increased risk.[55] A Swedish cohort study with follow-up ending in 2009 found an increase in the hazards of violent crime by 43% among individuals aged 15-24 years in on- compared to off-treatment periods within individuals, while lower and non-significant elevated effect estimates of treatment were found among older age categories.[60] However, a pharmacosurveillance study based on the US Food and Drug Administration Adverse Event Reporting System (FAERS) found consistent associations between SSRIs and violence events in a population consisting mainly of adults.[61] Importantly, there are lower baseline rates of violent crime among older populations,[62] suggesting that existing RCTs and cohort studies may suffer from low power to detect a risk among these populations. Evidence from further large-scale studies is therefore called for to investigate the age-related risks of violence associated with SSRI treatment, especially given that a majority of prevalent antidepressant users are middle-aged or older adults.

It is also important to understand whether the risk of violence varies according to time after start and end of SSRI treatment. There is evidence that this is the case for the risk of suicidal behaviour in relation to antidepressant treatment,[63] but there is a lack of evidence on this with regards to violence – particularly regarding the risk after the end of treatment.

1.4.2 Suicidal behaviour

Suicide is one of the leading causes of mortality in the developed world, especially among young people.[64] A particular area of concern is suicidality in children and adolescents undergoing antidepressant treatment. In the early 1990s, case reports showed that fluoxetine, the first SSRI licensed for sale, appeared to trigger suicidal thoughts in some patients[65] – based partly on challenge dechallenge rechallenge designs – followed by further evidence for other SSRIs.[65] By the early 2000s, the evidence for a risk of suicide among those aged under 18 years was compelling enough that, in 2004, the US Food and Drug Administration (FDA) issued a "black box" warning for the use of antidepressants in patients under the age of 18. In 2007, this warning was extended to individuals up until the age of 25.[66] Several European agencies followed suit.[67] However, studies of different designs and from different national settings show somewhat contradictory results, at least regarding the risk in adults. The extent of a suicide risk conferred by antidepressants in general, and SSRIs in particular, remains controversial.

RCTs investigating SSRI treatment in depression and non-OCD anxiety disorders have found a relatively consistent increased risk of suicidal ideation and attempts among children and adolescents. Notably, in the meta-analysis that lay basis for the first iteration of the "black-box" warning, the authors found a 66% increased risk of suicidal ideation or behaviour in SSRI treatment arms versus placebo among pediatric patients.[68] However, there was only a modest absolute risk difference – antidepressant treatment was found to increase the risk of suicidal ideation or behaviour in 1 to 3% of individuals, and no deaths by suicide occurred.[68] Recent systematic reviews of RCTs have also found substantially elevated risks of suicidal behaviour in SSRI-treated arms among children and young adults.[55 69] The RCT evidence for suicidality risk among adults treated with antidepressants is less consistent. A meta-analysis from 2005 of the association between SSRI treatment and suicide attempts across ages found more than a doubled odds in treated arms versus placebo.[70] A recent analysis of trials registered with the FDA also found an statistically significantly increased odds of suicidal deaths and attempts among adults.[71] By contrast, two other meta-analyses have found statistically non-significant protective effects among adults,[55 72] though the authors of one of these studies argued that harms are likely to be underestimated.[55] The different results across meta-analyses reflect that it is a challenge to estimate the risk of suicide associated with antidepressants in RCTs, especially among adults. The rarity of the outcome across trials means that small differences in analytic approach or inclusion of trials may have comparatively large impacts on the findings in meta-analyses.[71 73] Another issue is that RCTs

investigating suicidal outcomes during antidepressant treatment apply relatively extensive exclusion criteria – for example, they generally exclude individuals with a history of suicidal behaviour or ideation.[74 75] Evidence from real-world data is therefore important.

Ecological studies from the US and Canada have found that the decrease in antidepressant prescriptions directly following the black box warning coincided with an increase in completed suicide among children, adolescents, and young adults.[67 76] A Swedish study of suicide deaths among individuals aged 10-19 years found an increase in suicide death in the period after relative to before the black box warning, which mainly occurred in individuals not exposed to antidepressants immediately prior to death.[77] By contrast, another US study argued that the time-trends of antidepressant prescription and suicide rates among individuals aged below 18 years is consistent with the assumption that antidepressant treatment causes suicide.[78] However, ecological studies do not consider individual-level data, meaning that ecological bias is likely to affect findings and that associations on the group or country level may well be different on the individual level.[79]

Observational studies considering individual-level data represent an opportunity to study the risk for suicide in representative, real-world settings, with greater power than RCTs, and greater possibilities for confounding control than ecological studies. Prior observational studies have generally found an association between SSRI use and suicidality outcomes, including among adult users. In a UK study, Coupland et al.[63] found statistically significantly elevated hazard ratios (HRs) of completed suicide in the first 28 days since starting SSRI treatment, as well as in periods up to 84 days after discontinuing medication. In the case of attempted suicide or self-harm, they found statistically significantly elevated HRs during all periods of SSRI treatment, and for up to 28 days after stopping treatment. Similar patterns have been shown in a Danish cohort study,[80] where risk of attempted suicide was found to be highest within the first three months after collection of a prescription. A Swedish case-crossover study also found an approximately 3- to 4-fold increased risk of completed suicide after initiating SSRIs compared to control periods, with the highest risk 8-11 days after SSRI initiation, and with risks observed across ages.[81] By contrast, a nested case-control study based on US medical claims data found an almost two-fold increased risk (statistically non-significant) of attempted suicide among children and adolescent treated with antidepressants, and a statistically non-significant 15% lower odds among adults[82] – similarly to the results in two of the previously cited meta-analyses of RCTs.[55 72]

A remaining issue in any observational study is the impact of unmeasured confounding – particularly confounding by indication. This type of confounding occurs when the

characteristics that indicate an individual to treatment are also associated with the outcome of interest. For example, depression is the main indication for antidepressants, and is also a major risk factor for suicidal behaviour,[83] making it hard to parse apart the effects of the underlying disorder from the medication in observational studies.[84] A recent umbrella review found that, while there was consistent evidence of an association between antidepressants and suicide (attempted and completed) among children and adolescents from systematic reviews of observational studies, included studies had not sufficiently accounted for confounding by indication. Moreover, a prior study in Danish data has also found that the risk of suicidal behaviour is highest immediately prior to antidepressant initiation.[85] Further studies of different designs is called for to investigate the relationship further.

1.5 INDIVIDUAL VARIABILITY IN SSRI RESPONSE

It is important to consider individual differences in the risks and benefits of SSRI treatment. For example, features that have been suggested to predict response to SSRIs in depression include: the symptom profile of depression (e.g. age at onset and severity[86]); somatic and psychiatric comorbid disorders (e.g. substance use disorders[83]); demographic characteristics such as sex, age, and socioeconomic status[87]; biomarkers (such as blood levels of C-reactive protein[86]); genetic features[86]; and brain function (e.g. patterns of brain connectivity[88]). Therefore, overall efficacy or risk estimates cited in the preceding discussion may obscure groups with distinct benefit or risk profiles. Meanwhile, individual predictors may have weak or no predictive power on their own. For example, to identify particular high-risk groups for adverse outcomes during SSRI treatment – including complex combinations of several risk factors – prediction models could be developed to help guide clinical care.[89]

1.6 RISKS AND BENEFITS OF CO-MEDICATION WITH CNS DRUGS

Co-occurrence of one or more CNS drug class is becoming increasingly common in adult populations in the US[90] and Europe.[91] For example, US psychiatrist visits where patients were prescribed two or more CNS drugs increased from 42.6% to 59.8% between 1996-7 and 2005-6.[92] In psychiatric inpatients from Austrian, Swiss, and German clinics, the prevalence of CNS drug polypharmacy of at least two drugs increased from 74.1% in 2003 to 76.4% in 2005.[91] Among children and adolescents in the US, the percentage of visits to office-based physicians where more than one class of CNS drugs was prescribed increased from 14.3% in 1996-9 to 20.2% in 2004-7.[90]

The trend in increasing CNS polypharmacy may be warranted by the often severe and complex manifestations of mood and anxiety disorders in young individuals[93] and adults,[94] and/or reflect the presence of comorbidity between psychiatric disorders.[95] Adding other CNS drugs to antidepressant treatment may also represent treatment augmentation, particularly in treatment-resistant depression. The FDA has already approved five drugs for treatment augmentation of antidepressants, mainly atypical antipsychotics;[96] and there is evidence that further drugs show benefit for antidepressant augmentation. [97-101]

On the other hand, harmful drug-drug interactions (DDIs) may result from combining CNS medications. A study on children and adolescents from the US has found that, on average, combinations of two CNS drugs was associated with a 17% higher number of adverse outcomes compared with CNS monopharmacy.[102] There is pharmacokinetic evidence that SSRIs are inhibitors of cytochrome-P450,[103] which is involved in the metabolism of many types of medications in the human body.[104] Specifically, several types of SSRIs have been shown to inhibit the clearance of antipsychotics[105] and benzodiazepines, and to increase plasma levels of TCAs to different extents.[106]

Despite the possible risks and benefits of CNS co-medication or polypharmacy, the majority of evidence and guidelines regarding SSRI treatment relate to individual drugs, meaning that clinicians have little guidance on the appropriateness of specific drug combinations.[107]

2 AIMS

2.1 OVERARCHING AIM

To further the understanding of the association between SSRI treatment and severe behavioural outcomes, including when SSRIs are combined with other central nervous system (CNS) drugs.

2.2 SPECIFIC AIMS

Study I: To document the patterns of antidepressant use among children, adolescents, and young adults, including concurrent use of other CNS drugs with antidepressants.

Study II: To investigate the association between SSRI treatment and violent crime, including how the association varies by age and time since treatment start and end.

Study III: To investigate the association between SSRI treatment and suicidal behaviour, including how the association varies by age and time before and after treatment start.

Study IV: To screen for associations between initiation of different CNS drugs during SSRI treatment and suicidal behaviour.

3 DATA SOURCES AND MEASURES

3.1 DATA SOURCES

We have used data from Swedish national registers, linked through unique personal identification numbers.[108]

The main registers used in this dissertation are listed below.

Swedish Prescribed Drug Register (PDR): documents all dispensed pharmaceuticals, including ATC code, dates of dispensation, and the prescriber's practice and profession, in Sweden since July 2005.[109]

Total Population Register (TPR): documents demographic information for Swedish residents since 1968.[110]

Migration Register: covers emigration and immigration dates out of and into Sweden, and is a part of the TPR.[110]

The Cause of Death Register: documents dates and causes of death.[111]

The National Patient Register (NPR): documents inpatient care since 1973 and non-general practitioner outpatient care since 2001, including discharge diagnoses registered by ICD code.[112]

National Crime Register: includes crime convictions since 1973.[113]

Longitudinal integrated database for health insurance and labour market studies (LISA): includes information on disposable income, education level, unemployment benefits, civil status, social welfare payments, sick leave, and disability pension. It covers all individuals aged 16 years or above since 1990, and all individuals aged 15 years or above since 2010.[114]

These registers generally maintain a high quality. Only up to 2% of the PDR entries are likely to be invalid.[115] The NPR diagnosis data have good or excellent validity for disorders including bipolar disorder and schizophrenia,[116 117] while the validity is moderate to fair for depression.[14] Meanwhile, the TPR has effectively complete coverage of births and deaths that occur in Sweden.[110]

3.2 MAIN MEASURES

3.2.1 Antidepressant and SSRI subtypes

In study I, we considered all antidepressants (N06A). We identified the following subtypes: tricyclic antidepressants (TCAs: N06AA); selective serotonin reuptake inhibitors (SSRIs: N06AB); serotonin-norepinephrine reuptake inhibitors (SNRIs: N06AX16, N06AX21); monoamine oxidase inhibitors (MAOIs: N06AF, N06AG); and others (remaining N06A drugs).

In studies II-III, we considered SSRIs (N06AB) only as the exposure.

In study III and IV, we further considered the subtypes of SSRIs that were licensed for sale in Sweden during the study periods (Table 3.2.1).

Table 3.2.1. SSRIs licensed for sale in Sweden.

ATC code	Name
N06AB03	Fluoxetine
N06AB04	Citalopram
N06AB05	Paroxetine
N06AB06	Sertraline
N06AB08	Fluvoxamine
N06AB10	Escitalopram

3.2.2 Continuous treatment with SSRIs

In studies II through IV, SSRI treatment periods were defined using the assumption that prescriptions falling within 120 days of each other belonged to the same continuous treatment period, following the example of previous studies.[118] This is based on the Swedish "90-day rule" – oral medications are not routinely dispensed to cover a period of more than 90 days in Swedish psychiatric care.[118] We allowed for an additional 30 days between sequential prescriptions to accommodate for non-perfect treatment adherence. At the last prescription in a continuous treatment period, we added either 30 days (study IV), or the average number of days between prescriptions for the specific type of drug prescribed (studies II and III).

3.2.3 Other CNS medication

In study I, we defined use of other CNS medication concurrently with antidepressant use in 2013 as the presence of at least one dispensed prescription of the medication within six months of an antidepressant dispensation.

In studies II-IV, continuous treatment periods with other CNS medications were estimated in the same way as for SSRIs, but 30 days were added to the last dispensed prescription in a treatment period in all studies.

The non-SSRI CNS medications considered in each study are illustrated in Table 3.2.3 (shown at the 3rd level of the ATC code). In the studies included in this thesis, the medications are either considered as grouped variables, or at lower-level ATC codes.

Table 3.2.3. Non-SSRI drugs included in the thesis.

ATC code	Name	Studies included in
N02A	Opioids	I-IV
N03A	Antiepileptic drugs	I-IV
N05A	Antipsychotics	I-IV
N05B	Anxiolytics	I-IV
N05C	Hypnotics and sedatives	I-IV
N06A*	Antidepressants excluding SSRIs	I-IV
N06B	Psychostimulants	I-IV
N06D	Anti-dementia drugs	II and III
N07B	Drugs used in addictive disorders	I-IV

* excluding N06AB

3.2.4 Violent crime

We considered violent crimes (both sentences and arrests) of the following types: harassment, unlawful threats, stalking, coercion, assault, assault on official, robbery, sexual offences, arson, kidnapping, manslaughter, and homicide, based on prior work.[60]

3.2.5 Suicidal behaviour

We considered suicidal behaviour to consist of suicide attempts and deaths from suicide. Events of both known intent (ICD-10 codes X60-X84) and unknown intent (ICD-10 codes Y10-Y34) were included, based on prior work.[119 120]

3.2.6 Comorbid diagnoses

In study II, we investigated whether effect estimates varied by lifetime diagnoses of the following disorders (ICD-10 codes):

Attention deficit hyperactivity disorder (F90), alcohol use disorder (F10), anxiety disorder (F4), autism spectrum disorder (F84), bipolar disorder (F30-F31), conduct disorder (F91), depression (F32-F39), personality disorder (F60-F61), accidental poisoning by alcohol (X45), accidental poisoning by drugs and noxious substances excluding alcohol (X40-X44, X46-X49, T36-T50), schizophrenia spectrum disorder (F2), and substance use disorder excluding alcohol (F11-F19).

In study III, we considered whether results varied by receipt of diagnoses of: attention deficit hyperactivity disorder, autism spectrum disorder, bipolar disorder, or substance use disorder including alcohol (see ICD-10 codes above) before the month immediately preceding treatment initiation.

4 METHODS

4.1 PHARMACOEPIDEMIOLOGY STUDIES

4.1.1 Causal inference in epidemiology

Studies in medical research often aim to assess the risk or benefit of certain exposures. This implies that a causal contrast is of interest, rather than a statistical association alone. In epidemiological studies, causality is often expressed in the "potential outcomes" framework.[121] This holds that a causal effect is the difference in outcome between the factual outcome and the counterfactual outcome that would have been observed, had the subject received an exposure level different from that actually received. In practice, the potential outcome cannot be known, as we cannot measure the outcomes experienced by an individual under the exact same circumstances (including time) with different exposure statuses. Instead, causal effects are estimated by comparing the outcome between exposed and unexposed groups, on the assumption that each of these groups would have experienced the same risk of

the outcome as the other had they had the same exposure status as the other. In other words, we assume that there is "exchangeability", or comparability, between the groups.[121]

Randomized controlled trials (RCTs) are the gold standard for clinical research, as they allow for the greatest certainty regarding the comparability of groups. In RCTs, individuals are recruited at baseline and then randomized to receive different exposure statuses. If the randomization is carried out correctly and all study participants comply with their assigned exposure status, this ensures that both measured and unmeasured characteristics of the study participants are comparable across the different study arms. Comparing the outcome between groups then amounts to a causal contrast.

However, controlled trials are not always feasible. RCTs may not be ethical to carry out for certain research questions; are costly and time-consuming, and for that reason often have limited follow-up; and may have strict inclusion criteria – for example, antidepressant trials tend to routinely exclude individuals with past suicidal ideation or attempts.[74 75] Observational studies are therefore of interest to generate so-called "real world evidence"[122] that potentially has greater external validity. These studies can harness rich data sources to estimate causal contrasts in data where no formal randomization has occurred. Instead, exchangeability can be approximated by controlling for measured factors that affect both the exposure and the outcome (confounding). However, this requires strong subject matter knowledge, as it is impossible to prove with data alone that: a) a measured covariate is truly a confounder (and not, for example, a collider or effect mediator), and b) that there is no unmeasured confounding affecting results, i.e. that the observed adjusted association is similar to the true causal effect. A way to help structure thinking around what factors may be affecting the observed associations is to draw directed acyclic graphs.[123]

4.1.2 Exchangeability in pharmacoepidemiology studies

Observational pharmacoepidemiology studies are an important tool for generating generalizable evidence on treatment strategies from real word data. However, as with all observational research, the impact of confounding needs to be accounted for to ensure exchangeability. In particular, the study of treatment effects suffers from confounding by indication. This is when the disorder for which the drug is prescribed is also associated with the outcome of interest.[124] For example, the indications for SSRI treatment – such as depression – are in themselves associated with increased risk for suicidality and violence,[4 14] making it difficult to parse out the extent to which the treatment itself contributes to the risk as opposed to the underlying disorders being treated.

The ways of accounting for confounding can be grouped into conditional and marginal methods. The effect estimates from these methods may be similar in some scenarios, but may differ depending on aspects such as the incidence of the outcome, the number of confounders, and the chosen effect measure (due to non-collapsibility, where marginal effect estimates, such as the risk difference, may be different to conditional, or stratum-specific, effect estimates).[125-127] Conditional methods produce conditional effect measures; that is, effects of going from unexposed to exposed among individuals with specific combinations of covariates (that is, effects are "conditional", or conditioned, on measured covariates).[128] An example is regression adjustment, which is equivalent to taking a weighted average of the effect estimates of the exposure over strata of the confounder of interest (note that, if there are different effect estimates across strata of a confounder, interaction effects may be introduced, or the analysis may be stratified on the variable for which interactions exist). The resulting effect estimate of the exposure is interpretable as the effect of the exposure when all confounders are kept equal. Regression adjustment is used throughout this doctoral project, including to adjust for time-varying confounding. Additionally, in study II and III we have accounted for time-stable confounding – both measured and unmeasured – by stratifying on the individual.[129]

Meanwhile, marginal methods produce effect estimates representing the average effect of a whole study population going from unexposed to exposed.[130] For example, in RCTs, exchangeability of both measured and unmeasured confounders is ensured by randomising individuals to treatment or control groups. In observational settings, this can be approximated by estimating a propensity score for the probability of treatment with a drug given an array of measured confounders. For example, the analysis cohort may be weighted by the inverse probability of receiving the exposure levels that was actually received (Inverse Probability of Treatment Weighting; IPTW).[131] Individuals who receive treatment (or do not) despite a low (or high) probability of receiving it given their set of confounders are up-weighted in the analyses, and vice versa. A hypothetical cohort ("pseudo-population") is thus created, where individuals are "randomized" to their treatment based on their set of measured confounders.[132] An alternative way of producing marginal estimates is through regression standardization, where a marginal effect is derived from an initial regression analysis.[133]

It should be noted that marginal methods may be more suited than conditional methods in the presence of time-varying confounding. If a time-varying confounder is in part determined by the past treatment status, then conditioning on it in a conventional regression

model may induce collider-stratification bias.[134 135] In this case, marginal methods known as G methods (of which IPTW is one type) produce estimates without this bias.[134 135]

4.2 PHARMACOEPIDEMIOLOGY STUDY DESIGNS

We have employed several epidemiological study designs in the current thesis.

Cross-sectional studies consider associations between certain exposures and outcomes at a given point in time. A cross-sectional study design can also be used for descriptive studies, to assess e.g. prevalence of certain characteristics at a given time-point. We employ cross-sectional analyses in study I of this thesis, to assess the prevalence of antidepressant use by year, and its association with characteristics such as diagnoses and other medication use.

Case-control studies select cases as those who have experienced the outcome of interest, and controls as those who have not experienced the event. The likelihood that study participants had the exposure of interest prior to the event is then compared between cases and controls – in this sense, case-control studies are retrospective. Controls are usually matched to cases based on measured characteristics, with the possibility of selecting several controls per case. Case-control studies may be nested within cohort studies, where cases and controls are selected from the same prospective cohort. While not a strict case-control study, we did employ a matched design as part of study I, to assess the correlation between antidepressant use and 1) other CNS drugs, and 2) psychiatric diagnoses.

An extension of a matched study is the self-controlled case-series study, which is where each individual acts as his or her own control: a period at a given time before the outcome event is used as the control period for each case. A key advantage of this design is that it controls for all confounding – measured and unmeasured – that is stable over time in an individual. The assumptions are that exposures are intermittent or transient; that the occurrence of the event does not influence future exposure; and that recurrences of events are independent.[136] The implications of these assumptions for our studies will be discussed in the limitations section. We have used a variant of this design in studies II and III.

In addition to the study designs in this thesis, the emulated target trial is increasingly recognized as a helpful way to structure pharmacoepidemiology studies. With this approach, an observational study is designed to be as similar as possible to how an ideal RCT investigating the research question at hand would be (the "target trial").[137] This requires carefully defining and reporting features that would be crucial in the set-up of an RCT,

including: time zero of the study (for example, the date of a diagnosis), the causal contrast(s) of interest (for example, treatment versus no treatment with an SSRI), the endpoint of interest (for example, suicidal behaviour), and the outcome measures (marginal measures are usually favoured).

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4.3 STATISTICAL METHODS

4.3.1 Logistic regression

Logistic regression models a binary dependent variable against a number of independent variables[138].[138] The odds (the ratio of the proportion of study subjects with the outcome of interest to the proportion of study subjects without the outcome of interest) is modelled as a function of the independent variables on the logistic scale. The association measure of interest is usually the Odds Ratio (OR), which quantifies the ratio of the odds of the outcome of interest in the exposed group to the odds of the outcome of interest in the unexposed group. If the outcome is rare in the population (and in categories of the independent variables, if working with conditional estimates), the odds approximates the corresponding risk and the OR approximates the corresponding risk ratio.[139] However, if this "rare events" assumption does not hold, it becomes challenging to interpret what the odds represent.[139]

4.3.2 Cox Proportional Hazards regression

Cox Proportional Hazards regression is commonly used in survival analysis to model time-to-event data. An underlying time-scale is defined (e.g. age or calendar time since study entry) and the instantaneous risk (the hazard) of an event is modelled. The association measure of interest is the Hazard Ratio (HR), which quantifies the ratio of the hazard rate in the exposed group to that in the unexposed group. The hazard function for when all predictors are set to baseline values (the "baseline hazard") is not estimated in a Cox model, meaning no assumptions for the baseline hazard are required. However, one assumption of the Cox model is that the hazards in the different exposure groups are proportional over time. Even where the proportional hazards assumption is not met, the interpretation of a Cox model output can still be seen as a measure of average HR over the study time.[140]

4.3.3 Poisson regression

Poisson regression models the rate of an event over time. The outcome measure of interest is the Incidence Rate Ratio (IRR), which represents the rate of the event in the exposed group as compared to that in the unexposed group (note that "incidence rate" can be understood as

equivalent to "hazard").[140] A strong parametric assumption is that the rates of events is constant over defined time intervals (both baseline rate and comparator rate).[141] The key difference between a Poisson and a Cox regression model is that the former requires us to model the baseline hazard, which may be of interest in certain scenarios. We can model the baseline hazard using different approaches; if we model it using a piecewise constant model with very short time intervals, then the Poisson model gives equivalent estimates of exposure effects as a Cox model,[142] while the baseline hazard becomes highly uncertain.

4.3.4 Bayesian statistics versus frequentist statistics

Frequentist statistics are commonly applied in epidemiological research. Inference in frequentist statistics relies on the Central Limit Theorem, where specific data are understood as randomly drawn from a source population. The parameters estimated from each set of random samples have an asymptotic normal distribution, the average of which reflects the true population parameter. In a given sample, a Confidence Interval (CI) is given to the estimated sample parameter. If we consider, say, a 95% CI, then we can be confident that the CI contains the true population parameter 95% of the time if we were to conduct the analysis repeated times using different samples from the "source" population.[143 144]

By contrast, in Bayesian statistics, you use your available data to update your pre-existing (prior) estimate of what the value of the true parameter is.[145] In this way, you estimate a "posterior distribution" of possible values of the true parameter. From the posterior distribution you can then compute a Credible Interval (CrI). With a 95% CrI, you can say with 95% probability that the true parameter value lies within the CrI.[144] The interpretation of the CrI is therefore more straightforward than that of the frequentist CI.[144]

4.3.5 Accounting for multiple testing

Often, performing one or only a few hypothesis tests is not enough to answer all aspects of a research question. This is true on the level of an individual study, as well as on the level of a research field as a whole. However, there are problems with so-called multiple testing: as the number of tests increase, so do the number of chance findings that are statistically significant even in cases where the null hypothesis is true.[146]

Multiple testing is an issue in both frequentist and Bayesian statistics, though with somewhat different implications. In frequentist statistics, there are no clear limits to what tests should be considered in relation to one another when adjusting for multiple testing. In theory, all tests in the world might have to be accounted for one another.[146] Frequentist strategies for addressing multiple testing generally target the significance thresholds (p-

value) of tests – as in the case of the Bonferroni correction – and do not usually adjust effect estimates themselves.[146]

In Bayesian thinking, by contrast, any tests where either the hypotheses or the data are dependent are relevant to consider in relation to one another.[146] This sets at least theoretical bounds on the extent of multiple testing necessary (though, in practice, the number of dependent tests may be very large).[146] Another advantage of the Bayesian approach is that it allows for contextually informed adjustment of effect estimates.[146] This is because, in Bayesian statistics, external information may be taken into account when determining a plausible effect estimate – that is, information may be "borrowed" between dependent tests. In study IV of this thesis, we have opted to account for multiple testing in a Bayesian framework, using a multi-level modelling method proposed by Witte et al.[147]

5 SUMMARY OF INDIVIDUAL STUDIES

5.1 STUDY I: PATTERNS OF ANTIDEPRESSANT USE AMONG CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

5.1.1 Background

Antidepressants are the main pharmacological treatment for mood and anxiety disorders, which are common among young individuals.[1 148] While antidepressant use has become increasingly prevalent in several countries,[26 32 149 150] safety concerns regarding antidepressant treatment among young individuals have been raised, with evidence of increased risks of adverse outcomes such as violence, [151] suicidality, [55-57] and akathisia.[13]

It is important to document clinical patterns of antidepressant use among the young in order to direct future research on the harms and benefits of antidepressant drugs in a potentially vulnerable population. In this study, we therefore investigated antidepressant dispensation patterns – including source of prescription, type of antidepressant medication, treatment duration, and co-prescription with other central nervous system (CNS) drugs – among children, adolescents, and young adults in Sweden.

5.1.2 Methods

We selected a cohort of individuals aged under 25 and living in Sweden at some point between January 1st 2006 and December 31st 2013. From this population, we identified antidepressant users as individuals with one or more dispensed antidepressant prescriptions during the study period. For the last year of the follow-up (2013), we also randomly selected a control group of individuals who had no antidepressant dispensations that year, matched 1:1 on sex and year of birth to individuals dispensed antidepressants in that year.

We investigated the trend in prevalence of antidepressant use over the entire study period. For year 2013, we also documented the percentage of individuals: dispensing different antidepressant types (TCAs, SSRIs, SNRIs, MAOI, or other), receiving their prescription from different sources (primary care, psychiatric specialist care, or non-psychiatric specialist care), and experiencing antidepressant treatment for different durations (single prescription, <6 months' treatment, 6 to 12 months' treatment, or >12 months' treatment).

For year 2013, we further identified any CNS medication dispensed concurrently with the antidepressant medication, and described the proportions of individuals dispensing different numbers of concurrent CNS drug classes per year. We used logistic regression to calculate

the ORs of collecting specific CNS drug classes in antidepressant users during 2013 as compared to matched controls. Throughout analyses, we considered strata by age: children (age 0-11 years), adolescents (age 12-17 years), and young adults (age 18-24 years).

5.1.3 Results

5.1.3.1 Trends in antidepressant use over time

We identified 174,237 individuals aged under 25 who received one or more antidepressant dispensations during the study period. From 2006 to 2013, the prevalence of antidepressant dispensation increased from 1.4% to 2.1% in the complete cohort (relative change: 52.9%). Adolescents experienced the largest relative increase in the prevalence of antidepressant use, by 86.3% in females and 97.8% in males, while young adults had the highest prevalence of use throughout the study period (Table 5.1.3.1).

Table 5.1.3.1. Prevalence of antidepressant use in Sweden from 2006 to 2013.

		2006	2007	2008	2009	2010	2011	2012	2013	Relative Change (%)[a]	*P*[b]
All	Total (%)	1.4	1.4	1.5	1.6	1.7	1.8	1.9	2.1	52.9	<0.001
	Male (%)	0.9	1.0	1.0	1.1	1.2	1.3	1.4	1.5	60.8	<0.001
	Female (%)	1.8	1.9	2.0	2.1	2.2	2.3	2.5	2.7	48.9	<0.001
Children	Male (%)	0.05	0.04	0.04	0.05	0.06	0.06	0.08	0.08	78.5	<0.001
(0-11 years)	Female (%)	0.02	0.02	0.02	0.02	0.03	0.03	0.04	0.04	52.9	<0.001
Adolescents	Male (%)	0.6	0.7	0.8	0.8	0.9	1.1	1.1	1.3	97.8	<0.001
(12-17 years)	Female (%)	1.1	1.3	1.3	1.4	1.5	1.7	1.9	2.1	86.3	<0.001
Young adults	Male (%)	2.5	2.6	2.7	2.8	2.9	3.2	3.4	3.6	46.3	<0.001
(18-24 years)	Female (%)	5.2	5.4	5.4	5.5	5.7	6.0	6.5	7.0	35.4	<0.001

[a] Percentage difference in year 2013 compared with year 2006.

[b] Cochran-Armitage trend test.

5.1.3.2 Antidepressant prescription patterns in 2013

Females represented the majority of antidepressant users among adolescents and young adults, but the minority among children. Aside from this, there were similar patterns of antidepressant use across the sexes. For both males and females, SSRIs were the most common type of antidepressant. Specialist psychiatric care was the most common source of prescriptions among children and adolescents of both sexes (representing more than 70% of prescriptions), followed by psychiatric specialist care in all but adolescent females. By

contrast, 48.2% of female and 52.7% of male 18-24-year-olds received their prescriptions from psychiatric specialist care, followed by primary care. The majority of antidepressant users were treated with antidepressants for more than 12 months.

5.1.3.3 Polypharmacy with CNS drugs

The proportion of antidepressant users who experienced CNS polypharmacy (concurrent use of at least one additional CNS drug class) increased from 52.4% to 62.1% in the overall cohort over the study period, and adolescents experienced the biggest increase. Meanwhile, children saw the greatest increase in CNS polypharmacy of 2 or more drug classes – from 21.8% in 2006 to 38.7% in 2013.

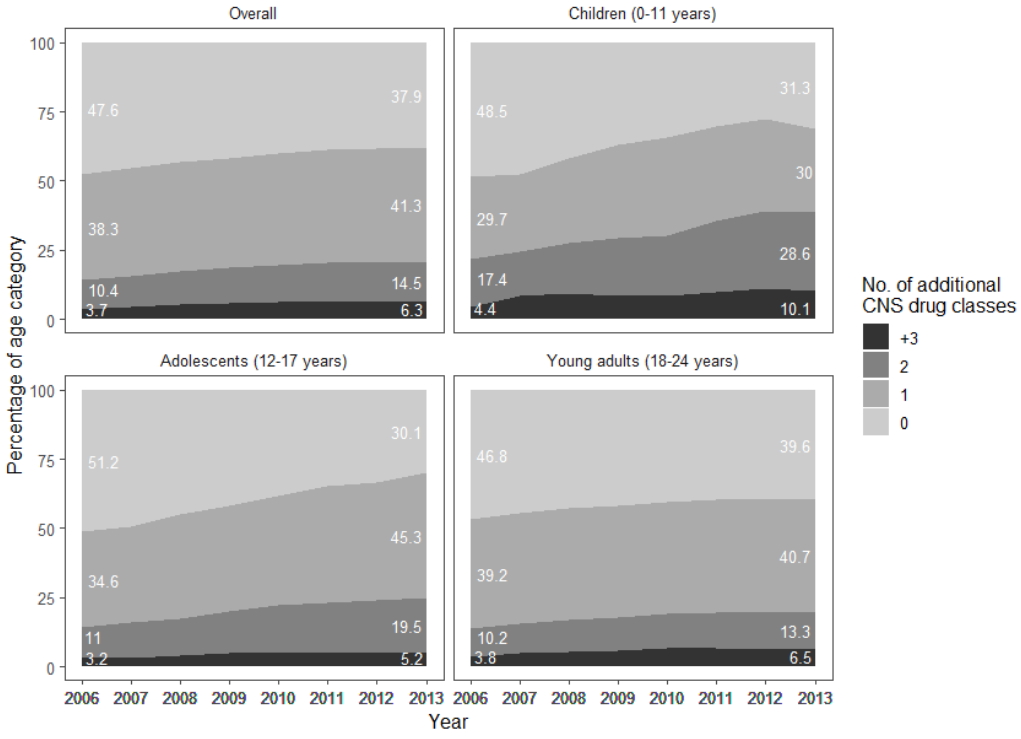

Figure 5.1.3.3 Percentage of antidepressant users with different levels of CNS polypharmacy 2006-2013.

Antidepressant users were more likely to receive other CNS drug classes than controls in 2013. The odds was greatest for receiving anxiolytics, hypnotics, and sedatives in antidepressant users versus controls across age categories (Table 5.1.3.3).

Table 5.1.3.3. Dispensation of common central nervous system (CNS) medications among individuals using antidepressants in 2013, by age group.

		Anti-psychotics	Anxiolytics, hypnotics, and sedatives	ADHD medication	Drugs used in addictive disorders	Opioids	Anti-epileptics
Children (0-11 years)	***User (N=833)***	158 (19.0%)	415 (49.8%)	397 (47.7%)	1 (0.1%)	14 (1.7%)	50 (6.0%)
	Control (N=833)	4 (0.5%)	13 (1.6%)	25 (3.0%)	0 (0.0%)	0 (0.0%)	5 (0.6%)
	OR (95% CI)[a]	52.0 (18.8, 142.7)	64.1 (36.4, 112.7)	31.6 (20.7, 48.4)	-	-	10.7 (4.2, 27.0)
Adolescents (12-17 years)	***User (N=10,033)***	1,300 (13.0%)	5,725 (57.1%)	2,756 (27.5%)	33 (0.3%)	486 (4.8%)	531 (5.3%)
	Control (N=10,033)	23 (0.2%)	195 (1.9%)	271 (2.7%)	2 (0.0%)	124 (1.2%)	51 (0.5%)
	OR (95% CI)[a]	65.2 (43.1, 98.6)	68.0 (58.6, 78.7)	14.4 (12.6, 16.4)	16.6 (4.0, 69.0)	4.1 (3.4, 5.0)	11.0 (8.2, 14.6)
Young adults (18-24 years)	***User (N=47,988)***	6,337 (13.2%)	25,848 (53.9%)	5,219 (10.9%)	947 (2.0%)	6,050 (12.6%)	5,258 (11.0%)
	Control (N=47,988)	192 (0.4%)	1,233 (2.6%)	550 (1.1%)	45 (0.1%)	1,642 (3.4%)	414 (0.9%)
	OR (95% CI)[a]	38.1 (33.0, 44.0)	44.4 (41.8, 47.1)	10.7 (9.8, 11.7)	21.5 (15.9, 29.0)	4.1 (3.9, 4.3)	14.2 (12.8, 15.7)

[a] Adjusted for sex and age (in one-year bands).

5.2 STUDY II: SSRIs AND VIOLENT CRIME

5.2.1 Background

There is concern regarding the possible link between SSRI treatment and aggression or violence. Evidence from a prior observational study in Swedish register data up to 2009,[60] as well as a meta-analysis of RCTs,[55] find statistically significant positive associations between SSRI treatment and violent crime or aggression, respectively, among young people, but non-statistically significant associations among older adults. Due to the low baseline rate of aggression outcomes – particularly the severe outcome of violent crime conviction – among older individuals, it is unclear whether an association between SSRI treatment and violence exists in older adults.

We therefore conducted a large register-based study with data up until 2013 to investigate whether SSRI treatment periods are associated with the risk of violent crime outcomes across ages. We also considered the risks in periods relative to start and end of treatment, to assess whether periods early after treatment start carry different risks than later periods, and whether risks persist after end of treatment.

5.2.2 Methods

We included all Swedish residents who had ever dispensed an SSRI medication between ages 15 and 60 years January 1st 2006 to December 31st 2013. We followed individuals from either January 1st 2006 or at attainment of age 15, depending on which occurred latest. We censored individuals on December 31st 2013, attainment of age 60, first emigration, or at death, depending on which occurred earliest. Individuals were not censored when the event occurred (conviction of a violent crime), and could experience several events during follow-up.

We applied Cox Proportional Hazards models to compare the hazard of violent crime conviction during periods on versus periods off SSRI treatment, stratified on the individual. We carried out these analyses in the overall cohort, in age strata, and in strata defined by lifetime psychiatric diagnoses. We also assessed whether HRs varied by time since treatment start and end. For age-stratified analyses, we considered the age categories 15-24 years, 25-34 years, 35-44 years, and 45-60 years.

5.2.3 Results

We identified 785,337 individuals for inclusion in the study. We found a statistically significantly elevated hazard of violent crime during SSRI treatment periods in the overall cohort (HR=1.26, 95% CI=1.19, 1.34), as well as in the different age strata. Only the 35-44-year-olds had a statistically non-significantly elevated HR (HR=1.15, 95% CI=0.99, 1.33; Table 5.2.3). We found no evidence of different associations across diagnosis groups. We also found increased hazards throughout all treated periods compared to periods before treatment start in the overall cohort. Hazards remained elevated over the first 84 days following end of treatment.

Table 5.2.3. Between- and within-individual associations between SSRI treatment and violent crime, by sex and age.

		Treated periods		Non-treated periods		Effect estimates	
Age	No. individuals[a]	No. events	Rate per 1000 person-years[b]	No. events	Rate per 1000 person-years[b]	Between-individual Hazard Ratio (95% CI)[c]	Within-Individual Hazard Ratio (95% CI)[d]
Overall	785,337	6,306	4.64	25,897	5.96	1.10 (1.06, 1.13)	1.26 (1.19, 1.34)
15-24 years	201,447	1,972	13.37	10,580	12.89	1.19 (1.13, 1.26)	1.28 (1.17, 1.41)
25-34 years	290,531	1,547	6.10	6,255	6.22	1.16 (1.10, 1.24)	1.35 (1.19, 1.54)
35-44 years	330,612	1,431	3.89	4,954	4.44	1.02 (0.96, 1.09)	1.15 (0.99, 1.33)
45-60 years	374,306	1,356	2.30	4,108	2.92	1.04 (0.97, 1.12)	1.25 (1.08, 1.45)

[a] Individuals may contribute to more than one age category during follow-up

[b] Not adjusted for any covariates.

[c] Adjusted for time-varying covariates: age, recent violent crime, use of non-SSRI antidepressants, benzodiazepines, and other psychotropic medications; non-time-varying covariates: sex, family income, highest attained educational attainment between the index person and its parents, county of residence, birth country, lifetime diagnoses, and history of violent crime before study entry.

[d] Adjusted for time-varying covariates: age, recent violent crime, use of non-SSRI antidepressants, benzodiazepines, and other psychotropic medications.

5.3 STUDY III: SSRIs AND SUICIDAL BEHAVIOUR

5.3.1 Background

The main safety concern with SSRI treatment regards the risk of suicidal behaviour in young people, mainly based on evidence from RCTs.[55] The evidence in older adults is less consistent.[55] Observational studies are an attractive alternative to RCTs, as they ensure greater generalizability and larger sample sizes to investigate the rare outcome of suicidal behaviour. Such studies have also found evidence of increased risk of suicidal behaviour among young individuals during SSRI treatment[80 82] and conflicting results among older adults.[63 81 85]

However, in an observational setting it is important to acknowledge that the disorders indicating SSRI treatment (mainly, mood disorders) are in themselves associated with greater risk of suicidal behaviour.[85] When assessing safety profiles, it is therefore important to consider that patients may already experience elevated risk of suicidal behaviour before treatment initiation.[84] Employing a national cohort of new SSRI users, we examined the risk of suicidal behaviour in periods leading up to and following SSRI treatment initiation.

5.3.2 Methods

We identified all individuals with an initiating SSRI dispensation at ages 6 to 59 years July 1st 2006 to December 31st 2013. We defined the initiating SSRI dispensation of a person as

an SSRI prescription collected after at least a one-year period (365 days) when the individual did not collect any SSRI medications.

In our main analysis, we investigated the risk of suicidal behaviour per month leading up to and following the initiating SSRI dispensation ("initiation analysis"; Figure 5.3.2). Follow-up started one year before treatment initiation, and ended one year later, end of SSRI treatment, emigration, death, or when an individual attained age 60, whichever occurred earliest.

In a complementary analysis, we followed individuals over time, allowing them to start and end SSRI treatment multiple times ("recurrent treatment analysis"; Figure 5.3.2). Follow-up began one year before the initiating SSRI dispensation; follow-up ended on 31st December 2013, first emigration, date of death, or when an individual attained age 60, depending on what occurred earliest.

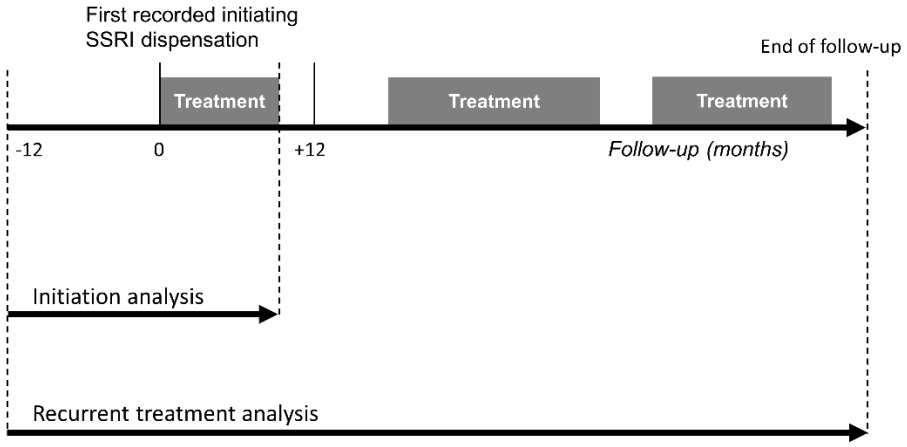

Figure 5.3.2. Cohort set-up.

Throughout analyses, we estimated within-individual incidence rate ratios (IRRs) using Poisson Regression models stratified on the inidvidual. For the initiation analyses, we applied two models: one using the month immediately preceding initiation (month -1) as the reference, and one using the month one year preceding initiation (month -12) as the reference. For the recurrent treatment analysis, we considered suicidal behaviour in periods off and on treatment. We divided off-treatment into the periods: more than 30 days before treatment start (reference category) and 30 days or less before treatment start. We divided on-treatment into the periods: 30 days or less after treatment start, 31-120 days after

treatment start, and over 120 days after treatment start. Throughout, analyses were stratified by age group (6-17 years, 18-24 years, 25-39 years, 40-49 years, and 50-59 years).

5.3.3 Results

We selected 538,577 individuals that had an initiating dispensation of an SSRI July 1st 2006 to December 31st 2013.

Initiation analysis

In the analysis with month -12 as reference, IRRs were statistically significantly increased from the month prior to initiation (month -1) up to the month one year after initiation (month +12). Month -1 had the highest IRR for suicidal behaviour in the overall cohort (IRR=7.35, 95% CI, 6.60-8.18) and across age categories. Following months (month +1 onwards) saw a gradual decline in IRRs from the level in month -1 to an IRR of 2.68 in month +12. In the analysis with month -1 as reference, months +1 (IRR=0.62) through +12 (IRR=0.37) had statistically significantly lower IRRs; again there was a gradual decline over time (Figure 5.3.3).

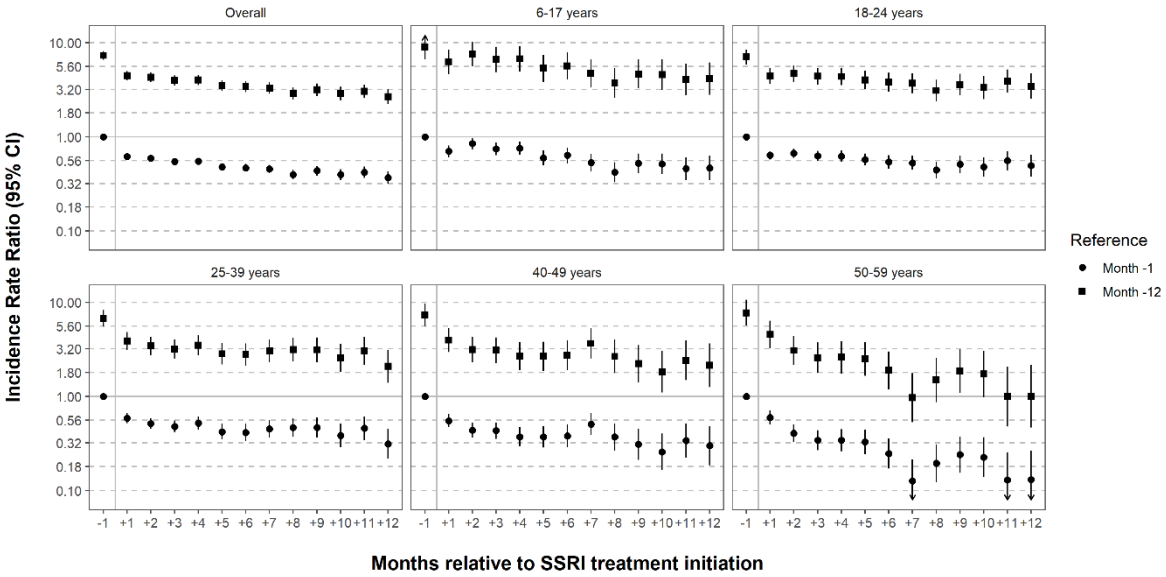

Figure 5.3.3. Within-individual incidence rate ratios of suicidal behaviour in months relative to first SSRI initiation.

Recurrent treatment analysis

The 30 days before start of SSRI treatment had the greatest IRR (3.25, 95% CI, 3.15-3.36 in the overall cohort), after which it declined steadily (to an IRR of 1.55 in the overall cohort) in the period more than 120 days after treatment start. The different age strata showed similar patterns.

5.4 STUDY IV: USE OF CNS DRUGS IN COMBINATION WITH SSRI TREATMENT

5.4.1 Background

While the use of other CNS medications concurrently with SSRIs is common, most guidelines focus on mono-treatment, meaning clinicians lack guidance on the risks and benefits of combining drugs.[107] A particular area of concern regarding many CNS medications, including SSRIs, is their effect on the risk of suicidal behaviour.

Co-prescription of drugs may be called for, such as for antidepressant augmentation[96] or the appropriate treatment of comorbidity. However, there is also a risk of harmful drug-drug interactions (DDIs).[152] Suicidal behaviour is an important marker of treatment benefits and risks. On the one hand, many of the disorders indicating an individuals to SSRIs increase the risk of suicidal behaviour in themselves,[15] meaning that a reduction in the risk of suicidal behaviour is a marker of treatment efficacy. On the other hand, there are concerns that SSRIs and several other CNS drugs may increase the risk of suicidal behaviour,[153] meaning an increase in the risk of suicidal behaviour during concurrent medication could indicate a potential harmful reaction and/or reduced treatment efficacy.

In this study, we applied a data-driven approach to screen for the risk of suicidal behaviour in periods after versus before specific CNS drugs are added to continuous SSRI treatment. For comparison, we also considered the risk of suicidal behaviour in periods before and after initiation of CNS drugs outside of SSRI treatment. The signals identified in this work are expected to help guide future research into the risks and benefits of CNS drug co-medication during SSRI treatment.

5.4.2 Methods

All individuals dispensing one or more SSRI medications at ages 6 to 65 years during July 1st 2006 to December 2013 were identified. For each individual, we estimated continuous treatment periods with SSRI medication and identified other CNS drugs that were initiated

during the SSRI treatment periods aged 6-65 years. Initiation of an additional CNS drug for a given individual was defined as dispensations after a 365-day period where the individual had not dispensed that particular drug. Only CNS initiations occurring more than 30 days after the start of the continuous SSRI treatment were considered (Figure 5.4.2). Any CNS drug that, across individuals, a) was initiated at least 1,000 times over the study period was and b) had at least 20 events in the 90-day period before or after initiation, was included in the analysis. For this set of included drugs, we also identified records of CNS initiations occurring at ages 6 to 65 years outside of treatment with any SSRI.

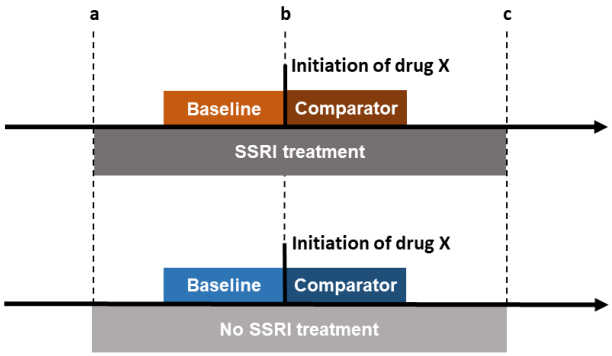

Figure 5.4.2. Illustration of CNS initiation during and outside of SSRI treatment. The time period between points a) and b), and between b) and c), is required to be ≥30 days.

Two-stage Bayesian Poisson regression was used to estimate IRRs and Credible Intervals (CrIs) of suicidal behaviour in the 90-day period after (comparator) versus before (baseline) initiation of a CNS drug, during SSRI treatment or outside of SSRI treatment (Figure 5.4.2). The first stage model was a conventional Poisson regression model, where the incidence rate in comparator versus baseline periods were compared in the group of individuals initiating a given CNS drug during or outside SSRI treatment. This model was adjusted for presence of baseline treatment with SSRI medications (0/1), age category (6-24 years, 25-34 years, 35-44 years, 45-54 years, and 55-65 years), and sex. The second-stage model was included to "borrow" information across third-level ATC groups of the initiating CNS drugs (e.g. "N02A"), and was a linear regression model where the coefficients for given combinations of baseline treatments (no/any SSRI treatment) and initiating CNS drugs were regressed on the ATC group. In this way, all estimates from our model were "shrunk" towards (pulled closer to) each other within the ATC groups, in order to reduce the likelihood of implausible false findings in the presence of multiple testing.[146 147] This was done because the drugs within the third level ATC groups are expected to carry

information about the effects of the other drugs in the group, given that the ATC classification system is based on the biological action of the drug and the disorder(s) the drug was developed to target.

The output of the model included the IRRs of suicide during SSRI treatment and outside of SSRI treatment. We also took the ratio of these estimates to assess whether interactions between SSRIs and the initiating CNS drugs were present.

5.4.3 Results

We selected 53 CNS drugs commonly initiated during SSRI treatment. We found that 267,721 individuals initiated at least one of them during SSRI treatment. Outside of SSRI treatment, 2,477,617 individuals initiated at least one of the included drugs.

Of the 53 drugs, 20 had statistically significant IRRs when initiated during SSRI treatment (Figure 5.4.3). Of these, 18 were associated with statistically significantly reduced risk of suicidal behaviour in periods after versus before initiation. Disulfiram, naltrexone, and acamprosate (all drugs used in alcohol dependence) had the greatest reduced risk (IRRs: 0.49, 0.50, 0.52, respectively). The two drugs with statistically significantly increased risk were benzodiazepine derivatives flunitrazepam (IRR=1.83, 95% CrI=1.11, 3.07) and alprazolam (IRR=1.39, 95% CrI=1.13, 1.71).

Six drugs had statistically significantly different IRRs when initiated during SSRI treatment versus outside of SSRI treatment. Four of these were associated with lower risk when initiated during SSRI treatment compared to outside SSRI treatment: zolpidem, zopiclone, propiomazine, and hydroxyzine. The two drugs with higher IRRs during as compared to outside SSRI treatment were codeine combinations excluding psycholeptics, and tramadol, though both of these drugs showed null associations with suicidal behaviour when initiated during SSRI treatment.

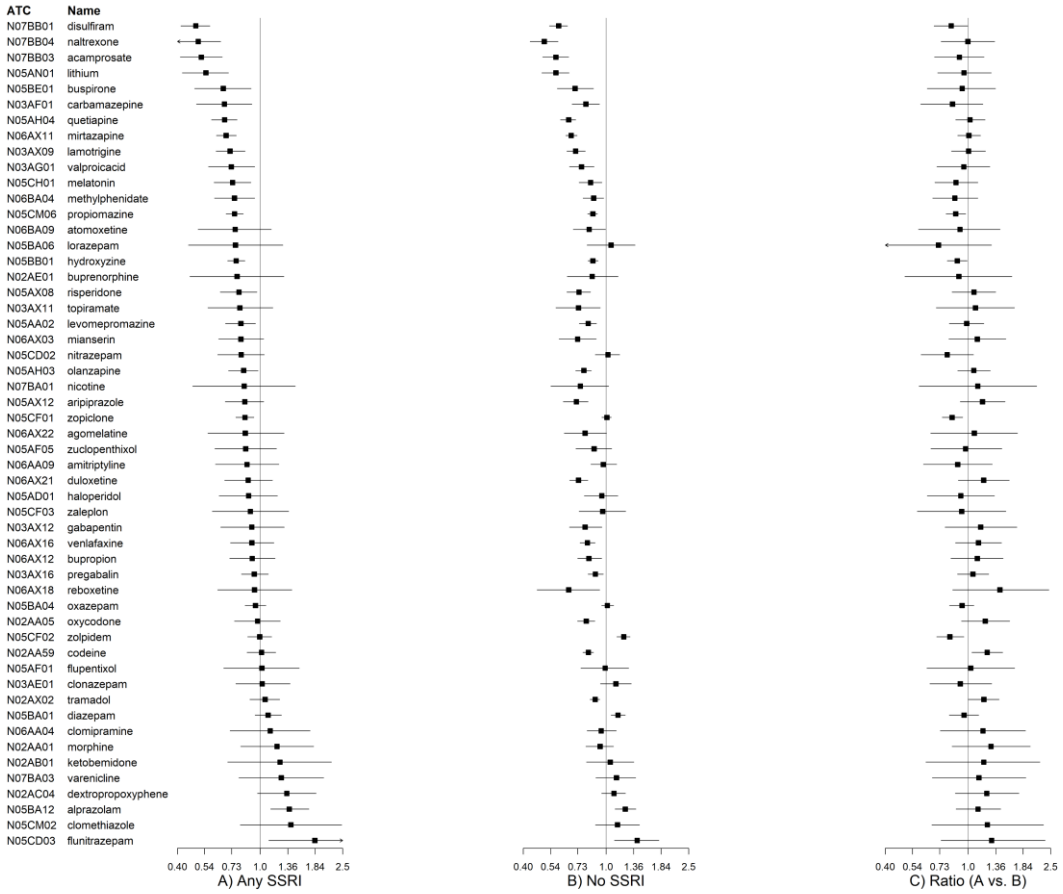

Figure 5.4.3. IRRs and credible intervals of suicidal behaviour associated with CNS drug initiation during treatment with and without any SSRI. N02AA59 represents codeine combinations excluding psycholeptics.

6 DISCUSSION

In this thesis work, we have investigated the association of SSRI treatment with two severe behavioural outcomes: violent crime conviction and suicidal behaviour. We have also examined patterns of antidepressant medication, and the possible impact of co-medication with CNS drugs on the risk of suicidal behaviour during SSRI treatment.

In study I, we documented the rise in prevalence of antidepressant use and polypharmacy of antidepressants with other CNS drug classes among children, adolescents, and young adults.

In study II, we found that SSRI treatment periods were associated with an elevated risk of violent crime convictions. The risk remained throughout SSRI treatment and up to 12 weeks after the end of treatment. As opposed to previous studies, we found that the hazard was elevated in older as well as younger adults.

In study III, we found that, while months during the first year of SSRI treatment were associated with elevated risk of suicidal behaviour as compared to the month one year before treatment initiation, the greatest risk of suicidal behaviour was in the month immediately before treatment initiation, and that the risk gradually declined over treatment time. This pattern was present across age categories, including among children and adolescents.

In study IV, we found that initiation with a number of CNS drugs during SSRI treatment was associated with a reduced risk of suicidal behaviour. Several of the signals correspond to prior evidence – the novel signals call for further investigation.

6.1 PATTERNS OF ANTIDEPRESSANT USE AMONG CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

6.1.1 Main findings

We found a number of notable patterns in antidepressant use among young individuals aged 0-24 years that were resident in Sweden during 2006-2013. Firstly, we found that antidepressant use increased across ages, with the greatest relative increase among adolescents. Secondly, SSRIs were the most commonly dispensed type of antidepressant, while most individuals were prescribed their antidepressant in psychiatric specialist care and were treated for more than one year. Thirdly, there were high and increasing levels of concurrent medication of antidepressants with other CNS drugs. Finally, antidepressant users

were more likely than population controls to collect additional CNS medications, with anxiolytics, hypnotics, and sedatives the most common additional drug class.

6.1.2 Interpretations and implications

The increase in antidepressant medication in this age group warrants attention. On the one hand, there is concern regarding the risk-benefit trade-off of antidepressant use in young people. On the other hand, the increasing trend in antidepressant use could be motivated by increasing levels of mood and anxiety disorders diagnosed among young individuals in Sweden.[154] Further research is needed to investigate how far the increase in antidepressant use in this age group represents appropriate clinical care of mood and anxiety disorders.

Several of the identified clinical patterns correspond to existing guidelines. For example, SSRIs was the most commonly prescribed antidepressant type, and are also the recommended first-line pharmacological treatment for depression among both adults and children in Swedish guidelines.[18]

Other features do not have support from existing guidelines. For example, a majority of antidepressant users received antidepressant treatment for more than twelve months. There is currently insufficient evidence and a lack of clinical guidelines regarding the impact of long-term antidepressant use.[23] Similarly, despite a lack of evidence on risks and benefits of polypharmacy among young individuals, we found that the prevalence of antidepressant users with concurrent treatment with other CNS drugs increased over the study period.[107 155] This development requires close monitoring and further research.[156 157]

6.2 SSRIs AND VIOLENT CRIME

6.2.1 Main findings

In this representative cohort of SSRI users in Sweden, we found statistically significantly elevated hazards of violent crime convictions throughout SSRI treatment periods, and up to 12 weeks following end of treatment, as compared to periods before treatment start. We found statistically significant associations in adults as well as young adults, in contrast to a prior observational study in Swedish register data with shorter follow-up.[60] Individuals with a history of violent crime and young men were the main contributors to the association, in a cohort where just under 3% of users were convicted for violent crimes.

6.2.2 Interpretations and implications

Our finding of an association between SSRI use and violent crime convictions suggest that clinicians should inform individuals at high risk of violent crime about this risk, and ask them to be observant of possible precursors, such as aggression. Individuals may then seek out medical attention regardless of whether their symptoms are caused by the SSRI treatment itself, by the underlying disorder indicating an individual for treatment, or a combination of the two. The fact that we find associations between SSRI use and violent crime even among older adults is potentially of public health interest, as a majority of antidepressant users are middle-aged or older adults.[8] We also confirm the association in younger individuals, where the baseline incidence of violent crime is highest. While we find that young men and individuals with previous violent crime appear to contribute most to the association, further research is necessary to investigate risk factors.

6.3 SSRIs AND SUICIDAL BEHAVIOUR

6.3.1 Main findings

In a nationwide study of Swedish residents initiating SSRI treatment, we found that the incidence rate of suicidal behaviour was highest in the month immediately preceding treatment initiation, with treated periods at least up to one year after initiation having statistically significantly lower risk by comparison. Still, compared with the month one year prior to initiation, all on-treatment periods had statistically significantly elevated risks. This pattern was consistent across age categories, including in children, adolescents, and young adults.

6.3.2 Interpretations and implications

Our findings suggest that, overall, SSRI initiation is not associated with an elevated incidence rate of suicidal behaviour after versus immediately before treatment initiation. However, incidence rates are elevated during on-treatment periods relative to the month one year prior to initiation. This confirms that attention should be paid to the risk for suicidal behaviour among patients treated with SSRIs, and that further work is called for to identify the risk factors for suicidal behaviour during SSRI treatment regardless of the underlying causal process. While the incidence rates gradually declined during on-treatment periods, the decline was slower and less marked in those aged under 25 years, though the risk reduction in the month immediately after versus before treatment initiation was similar

across all age groups. We cannot discount the possibility of an age effect here, as discussed further in section 6.5.2. We also cannot claim that our results are causal, or discount the possibility that individuals with certain risk factors may experience onset of suicidal behaviour as a consequence of SSRI treatment initiation.

6.4 USE OF CNS DRUGS IN COMBINATION WITH SSRI TREATMENT

6.4.1 Main findings

In this data-driven screening study, we found 18 CNS drugs that had a statistically significantly reduced incidence rate of suicidal behaviour when initiated during SSRI treatment. Only two of the investigated CNS drugs were associated with statistically significantly higher risk of suicidal behaviour after initiation. We found no evidence of adverse drug-drug interactions between SSRI treatment and the additional CNS drugs.

6.4.2 Interpretations and implications

Of the 18 CNS drugs with statistically significantly reduced IRRs of suicidal behaviour during SSRI treatment, several – including bupropion, mirtazapine, lithium, buspirone, and lithyronine – have previously been showed to be effective in individuals who do not respond to initial monotherapy with antidepressants.[97-101] Two of the 18 medications – olanzapine and quetiapine, both antipsychotics – are approved by the FDA for augmentation of antidepressants in treatment resistant depression.[96] This suggests that some of the novel signals of reduced suicidal behaviour risk that we detect could correspond to medications suitable in antidepressant augmentation strategies.

On the other hand, many of the drugs associated with reduced risk may simply reflect that comorbidities are appropriately treated. For example, it is known that addiction disorders are linked to higher risk of suicidal behaviour.[158] The fact that three drugs – acamprosate, disulfiram, and naltrexone – developed for treatment of alcohol use disorder are associated with the greatest reduced risk of suicidal behaviour may therefore reflect successful pharmacological treatment of addiction disorders. A further possibility is that the signals result from the process selecting individuals into treatment, as discussed further in section 6.5.2.

Only two drugs were associated with increased risk of suicidal behaviour – the benzodiazepines flunitrazepam and alprazolam. Prior research on benzodiazepines support an

elevated risk of suicidal behaviour during their use,[159 160] which has led to deregistrations or restriction in their use in several markets.

The novel signals of reduced suicidal behaviour risk call for further investigation to better our understanding of adjunctive therapy during SSRI treatment.

6.5 STRENGTHS AND LIMITATIONS

6.5.1 Strengths

The key strength of this thesis work is that it draws on representative nationwide registers, ensuring that results are generalizable to the entire Swedish population for the different age groups included in the studies. In study I, this gave us unique insight into the rise of CNS polypharmacy among young antidepressant users from a complete population cohort. In study II and III, this allowed us to investigate the risks of rare behavioural outcomes during treatment with SSRIs, including in age groups where power is usually low. In study IV, it allowed us to pick up on signals for suicidal behaviour risk across a range of CNS drugs co-administered with SSRIs, many of which are relatively rarely prescribed.

In studies II and III, we further employed within-individual comparisons, ensuring that we controlled for all unmeasured confounders – measured and unmeasured – that are stable within a person over time.

In study IV, we applied an approach that addressed multiple testing in a relatively attractive way.[146 147]

6.5.2 Limitations

Throughout the studies in this doctoral thesis, we used dispensed prescriptions as proxies for use, but cannot be sure that the purchased medications were consumed. All estimates should therefore be considered intention-to-treat,[60] which may lead to an underestimation of the effect estimates.[161]

We also did not have information on the indications for antidepressant prescriptions, or on diagnoses that were made in primary care. This meant we could not investigate in detail how our findings varied depending on which indication an SSRI was prescribed for. For the same reason, we do not have full information on an individual's healthcare contacts. Therefore, while our results are representative of full clinical populations undergoing treatment, they may obscure important clinical effect modifiers or mediators, the investigation of which

might lead to a better understanding of possible causal mechanisms.[162] The fact that we only have access to specialist care diagnoses also has implications for the interpretation of our age-stratified results. In Sweden, depression is routinely treated in specialist psychiatric care among individuals aged below 18 years, and in primary care at older ages. We therefore have better coverage of the diagnoses made in young individuals than in adults. In study III, where our outcome is defined based on specialist care diagnoses, we therefore cannot fully compare findings from individuals aged below 18 years to those from individuals aged 18 years or above.

Further, our treatment period definition may induce some misclassification regarding the length of medication exposure. An issue with our primary way of classifying treatment length is that it takes information from future prescriptions into account when assessing whether a given point in time constitutes an SSRI-medicated period. This is a potential issue, as the receipt of future SSRI prescriptions may be influenced by the outcomes we investigate (violent crimes or suicidal behaviour).[163] However, in studies II and III we conducted sensitivity analyses using an alternative treatment definition that relied minimally on information from future prescriptions by using the assumption that individuals were prescribed one SSRI pill per day. These sensitivity analyses produced very similar results to the main analyses. In future work, we could apply our method[164] of predicting prescribed daily dosage from prescription texts in order to create continuous treatment periods from SSRI prescriptions with minimized reliance on future prescription information. This would also allow us to investigate medication dosage. The impact of dosage is a clinically important question, and SSRI efficacy has been found to be dose-dependent.[46]

In studies II through IV, a key limitation is that we could not account for all time-varying confounding, including time-varying confounding by indication. In these studies, we look at the associations between medication treatment and selected behavioural outcomes. However, receipt of a prescription is associated with several time-varying factors that may also influence the risk of the outcome of interest, many of which we do not have measures for in our Swedish register linkage. For example, we do not have measures for time-varying changes in the severity of the disorders indicating an individual to treatment. We also do not have measures on the non-pharmacological treatments (e.g. psychotherapy) an individual might receive, or any of the other factors associated with accessing healthcare services (which dispensation of a medication is a marker of). This has particular implications for the age stratification of our results, as individuals under age 18 in Sweden are routinely treated in specialist care settings. They may therefore receive more extensive clinical attention than

adults, which are routinely treated in primary care. In study II and III, we did adjust the analyses for treatment with different non-SSRI CNS drugs. In study IV, where we used a screening approach, we did not account for other drugs taken in addition to SSRIs and the additional CNS drugs, meaning results may be biased by certain drugs systematically given in combinations with others.

Another issue regarding time-varying confounding in studies II and III is that we adjust for time-varying medication use in "standard" regression models. This is a potential problem, as the exposure to some of these confounders at a given time-point may be influenced both by unmeasured confounding and prior treatment status, and adjusting for them in a standard regression model may induce collider stratification bias,[135] as briefly discussed in section 4.1.2. However, in analyses without adjustment for time-varying CNS medication status, effect estimates in study II and III were similar, and the conclusions unchanged.

We employed variants of the self-controlled case series design in studies II and III. We used this design in part because it is hard to find an appropriate "external" control group for SSRI medication users – those who do not initiate treatment are expected to have different features to those who do, many of which we do not have measures for. However, this study design has some assumptions that our studies are not likely to fulfil. One assumption is that receipt of the medication should not be influenced by the occurrence of the outcome of interest,[165] as described in section 4.2. This assumption is not likely to hold in our case, as we can expect that some individuals are prescribed the medication, particularly an SSRI, because of a suicidal behaviour event; similarly, committing a violent crime may indicate psychiatric evaluation and subsequent SSRI treatment. In study III in particular, a consequence of this is that the risk reduction between the month immediately after versus before treatment initiation is possibly smaller than our results suggest (i.e. biased downward),[165] as the outcome rate is likely to be elevated prior to treatment because of this selection effect. For example, a previous study looking at the association between medication exposure and motor vehicle accidents considered the four week period before initiation of medication separately to allow for a period where the occurrence of an accident may have selected individuals into medication treatment,[166] and the authors did not place emphasis on the difference in event rates in the period immediately after versus before treatment start. However, in our case our outcome – suicidal behaviour – is associated with the very disorder SSRIs are indicated to treat.[84] Depression is episodic, and therefore the period immediately prior to treatment start may be more relevant as a reference period in our study III.

Another assumption of the self-controlled case series design is that prior events do not influence the likelihood of further events.[136] This assumption may be violated in study III given that prior suicide attempts have been found to be predictors of further events.[167] A suggested solution to this problem is to only consider the first occurrence of an event.[136] Still, in our study III, about 76% of those who engaged in suicidal behaviour during the follow-up had only one event, and another 15% had two events, suggesting that if this assumption were violated it would likely not pose a considerable problem.

Further, our designs comparing periods after to before SSRI treatment initiation in study III and IV means we cannot investigate the risk of incident suicidal behaviour in the subgroup of individuals who have no prior history of such events before treatment initiation. These designs also require individuals to have survived until medication dispensation, meaning we cannot include individuals who die by suicide before they initiate treatment. This might bias the effect estimate of the comparison between the period after to before initiation upwards, as individuals by definition can only commit suicide after medication initiation.

Finally, given the limitations noted above and the observational nature of our data, it should be emphasized that our studies cannot be used to infer causality. Further research is called for to triangulate the findings presented in this thesis work.

6.6 FUTURE DIRECTIONS

6.6.1 Alternative observational designs

The present thesis has focused on self-controlled designs, which have their strengths and limitations (discussed in section 6.5). Alternative designs are important to triangulate our findings. In particular, a useful design to complement findings from studies employing within-individual comparisons is to emulate a target trial, as discussed in section 4.2. The goal is to create an observational study that as closely as possible mirrors an ideal target trial for the question at hand, in order to minimize common biases that may arise in observational research (such as immortal time bias).[137] For example, when assessing the association between SSRI initiation and suicidal behaviour in depression, individuals that receive a depression diagnosis may be selected, and followed over time from their diagnosis. Individuals who do and do not initiate an SSRI may then be compared in terms of their risk of suicidal behaviour. Marginal methods are generally applied to analyse the data, such as G methods (RCTs themselves generally produce marginal effect estimates). If time-varying

confounding is considered, the use of G methods is particularly motivated to avoid collider-stratification bias,[135] as described in section 4.1.2.

6.6.2 Prediction models

It is of clinical interest to develop prediction models that help identify which individuals are more likely to experience severe behavioural outcomes during SSRI treatment, regardless of whether the events are caused by medication exposure or not. This would allow high-risk individuals undergoing SSRI treatment to be given appropriate clinical attention, and is arguably most pressing in the case of the lethal outcome of suicide.

However, prior studies have shown that it is challenging to predict suicide due to the rarity of the outcome.[168] In general, it appears that existing suicide prediction models are better at identifying those that are very unlikely to engage in suicidal behaviour, than at predicting who is very likely to.[168] While the overall classification accuracy of existing models is good (as measured by area under the curve: AUC), the ability of the models to correctly identify which individuals will go on to have an event (the positive predictive value, or PPV) is generally low.[169] In light of this, there have been calls to use suicide risk prediction models as a first instance of a multi-stage approach.[168] In such a scenario, the suicide prediction model would act as a screening tool to exclude individuals that are very unlikely to commit suicide from further assessment. Among those identified to have an average or above-average risk in the risk prediction model step, more in-depth clinical evaluations could be employed to help identify individuals at particularly high risk.[168] It is also possible that leveraging new data sources with a broad set of available predictors and applying advanced analytic methods may improve the performance of suicide risk prediction models.[168]

6.6.3 Developments in pharmacological treatments of mood and anxiety disorders

The presented thesis mainly considers treatment with SSRIs, which currently constitute the main pharmacological treatment for depression and anxiety. However, there is growing research interest in new pharmacological treatments of depression, anxiety, and substance use disorders. The drug esketamine – which has dissociative properties at non-anaesthetic doses – was approved by the US Food and Drug Administration (FDA) in 2019 for use in treatment-resistant depression as a new type of antidepressant (ATC code N06AX27).[170] Further, the classic psychedelic psilocybin has shown promise for the treatment of a range of psychiatric disorders in a series of recent small-scale trials,[171-173] in particular when administered in one or a few high-dose therapist-assisted sessions where an intense psychedelic experience, often

involving ego-dissolution, is produced. In a recent small (N=59) randomized controlled trial (RCT) employing a head-to-head comparison between high-dose-psilocybin- and escitalopram-assisted therapy in depression over six weeks' follow-up, there was greater response and remission in the psilocybin arm.[174] However, neither outcome measure was statistically significantly different from that in the escitalopram arm,[174] and the authors call for larger trials with longer follow-up. Research interest in these therapies is high, with several further trials currently registered with the FDA.[175] More research is required to better understand their risk and benefit profiles.

The research into psychedelic therapies is expected to yield new insights into psychiatric disorders and their treatment. For example, they suggest that psychedelic therapies may be effective in the treatment of disorders such as depression, anxiety, substance abuse, and OCD because, when administered in a safe clinical environment, they allow for rapid relaxation of learned assumptions, particularly related to avoidance behaviour.[176] [177] This is similar to what psychological treatments such as CBT aim to achieve,[176] but with the aid of a psychedelic experience that for a short timespan increases communication between different brain regions[178] and thus allows for new associations to be formed.[176] This corresponds to evidence that individuals with depression have higher connectivity within the default mode network (DMN) but lower connectivity between the DMN and other brain networks,[179] and that individuals with treatment resistant depression are more likely to have a hyperconnected DMN than individuals who respond to current antidepressant treatments.[88] Importantly, much of the previously cited research indicates that only a few high-dose administrations of a psychedelic could be enough to produce lasting improvement, as opposed to the often long-term treatment required with current antidepressants such as SSRIs.

However, psychedelic therapies are highly personnel-intensive and may not be feasible or desirable in all patients seeking psychiatric care. SSRIs and other common antidepressants will likely continue to be important treatment alternatives in psychiatry for the foreseeable future.

6.7 ETHICAL CONSIDERATIONS

The ethical requirements of research on natural persons, enshrined in Swedish law (Etikprövningslagen; SFS 2003:460), prescribe that research: do good, minimize harm, involve informed consent from study subjects, and ensure a fair distribution of risks and benefits between persons involved in the research. Based on these tenets, the Stockholm

Regional Ethics Committee has given ethical approval to the data linkage upon which the analyses in this thesis are based. This applies to each constituent paper of the thesis – no further ethical permits are required, as explained below.

The research presented in this thesis aims to provide benefit to the scientific and clinical communities by providing evidence on important topics relating to SSRI treatment in representative, "real-world", samples. Our large observational cohorts provide the opportunity to address questions that may be costly, impractical, or unethical to investigate through the use of RCTs.

Regarding possible harms, all included studies consider sensitive personal data from Swedish residents, including detailed information on diagnoses, socioeconomic status, and family relationships. If this information were to end up in the wrong hands, it could have dire consequences, making the minimization of possible harm important. This is achieved through "pseudonymisation" of the individual-level data from the registers, meaning that information cannot be linked to identifiable natural persons without access to an identification key held by Socialstyrelsen. The Swedish Official Statistics Act states that this waives the usual need for informed consent. Further, the final outputs of the research, usually in the form of published papers, only include summary statistics that preclude identification of individuals. Despite this, data security is of great importance, and has been ensured by keeping all individual-level data on secure servers at all times.

The studies in this thesis are also expected to have a fair distribution of risks and benefits. Virtually all Swedish residents are included in the registers that lay basis to the research, meaning that the results of the studies may benefit large numbers of people, at present and in the future, including those that participate in our cohorts. No vulnerable group is exploited by this research, and the studies entail observational analyses of historic data, meaning that the research at no point interferes with the lives of the study subjects.

Finally, it is important to consider the controversial subject of the presented thesis. The risks of antidepressant use in general, and SSRI treatment in particular, is the topic of extensive debate among researchers, clinicians, and the public. It is important to understand the risks of SSRI treatment on the one hand, but on the other, our findings should not be presented in such a way that clinicians unnecessarily withhold SSRI treatment from patients who might benefit from it. Any results suggesting benefits of SSRI treatment should also be understood in the context of the limitations of the study on the one hand, and that of Swedish clinical care and non-pharmacological care alternatives on the other. Throughout the discussion sections

of the included studies, we have attempted to convey a balanced discussion of how the results may be interpreted, and what the implications are – and are not – for clinical practice.

7 CONCLUSIONS

In this thesis, we document the increasing prevalence of antidepressant use among young people in Sweden, as well as the rise in polypharmacy of other CNS drugs with SSRIs. Further, we find that SSRI treatment periods are associated with an elevated risk of violent crime conviction across young and middle-aged adults, suggesting that attention should be paid to precursors of violent behaviour in high-risk individuals taking SSRIs, regardless of age. We also find that the incidence rate of suicidal behaviour is greatest in the month immediately preceding the start of SSRI initiation, though on-treatment periods up to one year after initiation have an elevated rate as compared to the month one year prior to initiation. Crucially, we cannot discount the possibility that SSRI treatment precipitates suicidal behaviour in individuals with certain risk factors; meanwhile, the descriptive finding of increased risk of suicidal behaviour during SSRI treatment compared to the one-year baseline suggests attention should be paid to precursors of suicidal behaviour in individuals initiating SSRI treatment. Finally, we find a number of CNS drugs associated with reduced risk of suicidal behaviour when initiated during SSRI treatment, presenting possible targets for further study on their use in conjunction with SSRIs. Additional research is necessary to triangulate our findings, assess whether the associations we find are causal, and identify key groups at high risk of severe behavioural outcomes.

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